DISCUSSION POINTS RE: EPA RISK ASSESSMENT SCIENTIFIC ISSUES

1. Isn't it a fact that 24 of the 30 studies reviewed by the EPA, and on which it based its risk assessment calculations, originally reported no statistically significant overall increased risk for spousal smoking?

Discussion: The EPA should respond in the affirmative.

The concept of "statistical significance" is important because it permits a scientist to infer either that the data in a study support or do not support a given hypothesis. For the studies on spousal smoking and lung cancer, the data in 24 of 30 studies reviewed by the EPA are compatible with the hypothesis that there is no overall association between spousal smoking and lung cancer.

Typically, when results do not achieve statistical significance, further analysis of the data is not meaningful or productive. Apparently, the EPA does not ascribe to this accepted statistical principle. While data from the six remaining statistically significant studies permit the scientist to reject the hypothesis of no association, the scientist must further investigate whether the statistically

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significant association is due to the exposure in question or to some other factor.

2. Isn't it true that of the 11 U.S. studies reviewed by the EPA, not one originally reported an overall statistically significant risk?

Discussion: The EPA should confirm that none of the eleven studies reviewed by EPA originally reported an overall statistically significant risk.

Moreover, even when the EPA recalculated the statistical confidence limits for the 11 U.S. studies, only one of those studies reportedly achieved statistical significance. However, as indicated above, the raw data in the 11 studies do not permit chance to be effectively ruled out.

3. Isn't it true that of the 30 studies the EPA considered, 11 included estimates of workplace exposures, of which nine reported no statistically significant increased risk for nonsmoking females?

Discussion: The EPA should clearly respond in the affirmative.

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If the data on workplace exposures are pooled in a meta-analysis, the risk estimate is below 1.00 (unity), which indicates no positive association between reported workplace exposures to ETS and lung cancer in nonsmokers. However, the Risk Assessment did not consider those data.

4. Isn't it a fact that the EPA omitted from its ETS risk calculation data from the NCI-funded Brownson, et al., study, one of the largest and most recent studies on ETS exposure and lung cancer, which found no increase in risk from exposure to ETS?

Discussion: The EPA should confirm that it has not included the Brownson study in its calculations.

This case-control study is among the largest conducted on reported ETS exposure and lung cancer incidence. It includes 432 "lifetime" nonsmokers and 186 exsmokers, and 1,402 controls.

* An OR of 1.0 (95% CI 0.8-1.2) was reported for spousal smoking in nonsmokers (218 cases and 598 controls). This odds ratio is not statistically significant.

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The full citation for this study is:

Brownson, R.C., Alavanja, M.C.R., Hock, E.T., and Loy, T.S. "Passive Smoking and Lung Cancer in Nonsmoking Women," American Journal of Public Health 82: 1525-1530, 1992.

5. **Isn't it true that if the EPA had included the Brownson study, its risk assessment would not have found a statistically increased risk of lung cancer due to exposure to ETS?**

Discussion: The EPA should unequivocally answer yes.

If the Brownson study is added to a meta-analysis of the U.S. ETS-lung cancer studies, and if the EPA's method of adjustment for misclassification is applied to the study, the resulting summary risk estimate for all U.S. studies does not exceed 1.07, a risk estimate which is not statistically significant.

6. **In light of the above, isn't it true that the EPA would not have classified ETS as a Group A carcinogen had the EPA used the methodologies and guidelines it employed in all its previous risk assessments?**

D scussion: The EPA's answer should be yes.

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The EPA has established a precedent-shattering framework for the ETS and other future risk assessments. As proclaimed by Dr. William Farland, from EPA's Office of Health and Environmental Assessment to the Science Advisory Board's IAQTHEC meeting on July 21, 1992:

> This (the ETS risk assessment) is a high visibility assessment . . . because of its implications for the future of the way we do business. (Meeting transcript, at I-31.)

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> First of all, we have a focus on human data which is fairly unique in terms of dealing with environmental pollutants. (Meeting transcript, at I-33.)

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> Another fairly unique situation with regard to environmental risk assessments is we've taken the opportunity to use some new techniques, meta-analysis for lung cancer, that we think will be important to us in terms of combining information from various studies as we do risk assessments in the future. (Meeting transcript, at I-34 .)

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> So, we think that there are some interesting and important features and <u>an opportunity to do some innovative risk assessment work in this particular assessment</u>. (Emphasis added.) (Meeting transcript, at I-35.)

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So these are all features of this particular assessment that we think are going to have a great impact on the way we do future assessments in the Agency. . . . (Meeting transcript, at I-36.)

If the EPA had followed its own 1986 draft guidelines, it would have included: (1) a hazard evaluation which would have examined data regarding the physical and chemical characterization of ETS, as well as the results from published animal inhalation studies and in vitro studies; (2) an exposure evaluation which would have included the data from well over 100 studies in the published literature which monitored ETS constituents in the air of public places and workplaces; (3) a dose-response evaluation which would have included an examination of the actual data reported in the epidemiologic studies on spousal smoking; and (4) a risk characterization which would have included the range of uncertainty in numbers of lung cancer deaths reportedly attributed to ETS exposures. The guidelines also require, for the evaluation of epidemiologic studies, that chance must be ruled out statistically (i.e., the results should be statistically significant), and that all possible biases and possible confounding factors in such

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studies are to be considered. The EPA's current strategy to classify ETS as a Group A carcinogen based solely upon epidemiologic studies would have failed had they carefully adhered to their own guidelines.

7. Isn't it true that if the EPA were to subject chlorinated water, the ordinary tap water consumed by most Americans, to the exact same methodology applied to ETS, chlorinated water would also be a Group A carcinogen?

Discussion: EPA must clearly answer yes.

According to the results of a meta-analysis of reported data on the chlorination of water and chlorination by-products and cancer incidence, published in the American Journal of Public Health (July 1992), the authors reported that "a sample meta-analysis of all cancer sites yielded a relative risk estimate for exposure to chlorination by-products of 1.15." These results were statistically significant, as were results reported for "organ-specific neoplasms" such as bladder cancer and rectal cancer. The meta-analysis was based upon the adjusted relative risk estimates from epidemiologic

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studies, precisely the same basis used in the EPA risk assessment on ETS. The estimated results were reportedly statistically significant, even after the apparent adjustment for confounding factors.

The full citation for this study is:

Morris, R.D., Audet, A.-M., Angelillo, I.F., Chalmers, T.C., and Mosteller, F., "Chlorination, Chlorination By-products, and Cancer: A Meta-analysis," American Journal of Public Health 82(7): 955-963, 1992.

8. **Isn't it true that the NCI has completed a major study that finds poor diet among non-smoking women is a significant risk factor for lung cancer? If that's true, doesn't this mean that all ETS studies that didn't take diet into consideration must be re-evaluated?**

Discussion: **A finding by the NCI that poor diet among nonsmoking women is a significant risk factor for lung cancer should compel EPA to answer yes.**

Several of the published studies on spousal smoking considered by the EPA also have adjusted for the importance of diet. While the results are mixed, several suggest that a healthy diet, or, conversely, the avoidance of a poor diet containing fat and

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spicy foods, will affect risk estimates for nonsmokers married to smokers. Other studies suggest that diet is an independent risk factor for lung cancer.

9. Isn't it true that this is the first time the EPA has classified any substance a Group A carcinogen based on such weak epidemiological data and without corroborating animal data?

Discussion: EPA must respond in the affirmative.

This is the first EPA risk assessment based solely upon epidemiologic data in which a substance has been designated a Group A carcinogen. Public comments on the risk assessment by scientists pointed out that the epidemiologic data on spousal smoking, when taken as a whole, do not convincingly support a Group A carcinogen classification. Most of the studies are not statistically significant, and study biases and confounders (e.g., occupation, diet, heredity, etc.) were not effectively ruled out as contributing factors to the reported associations between spousal smoking and lung cancer. The summary risk estimate achieved by combining those studies

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is very low (less than 1.20), which is deemed "weak" by epidemiologists and statisticians. Moreover, the Group A carcinogen classification has not been corroborated by any published animal inhalation studies.

10. Is 't it true that this is a case of EPA "adjusting science to fit policy" as it was criticized for doing in its audit report Safeguarding the Future by excluding studies that don't fit its objective, changing the confidence level from 95% to 90% and not disclosing its methodologies for external analyses and verification?

Discussion: The EPA's SAB review draft risk assessment on ETS (May, 1992) excluded from consideration over 25 studies on childhood respiratory disease and parental smoking which did not report an affect from parental smoking. It also excluded from its analysis published criticisms of epidemiologic studies on spousal smoking and lung cancer. Perhaps even more important, it presented a meta-analysis of the available epidemiologic studies on spousal smoking which is not readily reproducible, and one in which the confidence interval was narrowed from the

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scientifically accepted 95% level for statistical significance to a 90% level.

11. Why has the EPA undertaken a re-analysis of the published data on ETS and lung cancer?

Discussion: The EPA will argue that its re-analysis of the data was necessary in order to determine more precisely an effect from ETS exposures.

For example, the EPA will undoubtedly point to the "profound effect" on lung cancer incidence from reportedly "high exposures" to ETS that it discovered during re-analysis of the data. Seventeen of the 30 studies examined by the EPA present data on individuals who reported "high" exposures to ETS. The EPA re-analyzed those data and claimed that they displayed a clear, positive trend, i.e., every one of the high exposure groups in the 17 studies exhibited an increased risk for lung cancer.

While this argument may, at face value, appear compelling, it is a clear example of what statisticians call "data-dredging." It is important to note that the raw data which provide the basis

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for the EPA's re-analysis are consistent with the hypothesis of "no association." Twenty-four of the 30 studies on spousal smoking report no statistically significant overall association between spousal smoking and lung cancer in nonsmokers. Moreover, the raw data presented in the published studies do not indicate significant dose-response trends (i.e., they do not indicate statistically significant relationships between increases in exposure to ETS and increases in disease incidence). In short, the EPA has applied what statisticians call "trend tests" to data which do not achieve statistical significance and which are consistent with the hypothesis of no association between spousal smoking and lung cancer.

Thus, EPA's "re-analysis" of the data on spousal smoking and lung cancer appears to have been undertaken, not in an attempt to test the hypothesis of whether or not ETS is associated with lung cancer in nonsmokers, but to provide support for its claim that ETS <u>is</u> associated with an increased risk of lung cancer. Its re-analysis of the data is the reverse procedure used in scientific inquiry. The EPA starts with what it presumes to be a given, namely, that ETS causes lung cancer, and then it

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applies meta-analysis, makes background adjustments for exposure to ETS, changes statistical procedures, and re-analyzes high exposure level data to support its position.

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